Journal of
Cardiology & Cardiovascular
Surgery

Original Article

DOI: 10.51271/JCCVS-0017

Hemodynamic effects of etomidate anesthesia induction in diabetic and non-diabetic patients: Importance of heart rate variability in early detection of cardiac autonomic dysfunction

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Cite this article: Koç A, Uzman S. Hemodynamic effects of etomidate anesthesia induction in diabetic and non-diabetic patients: Importance of heart rate variability in early detection of cardiac autonomic dysfunction. *J Cardiol Cardiovasc Surg.* 2023;1(4):61-65.

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Received: 07/03/2023 ◆ **Accepted**: 25/10/2023 ◆ **Published**: 29/12/2023

ABSTRACT

Aims: Cardiovascular diseases represent the primary cause of perioperative morbidity among diabetic patients. Etomidate, an anesthetic agent with minimal cardiovascular effects, is commonly used in these patients. Diabetic patients often experience cardiovascular autonomic neuropathy, a severe complication of diabetes. In recent years, measuring heart rate variability has become increasingly important for early detection of cardiac autonomic dysfunction. The aim of this study was to compare the hemodynamic effects of etomidate anesthesia induction between diabetic and non-diabetic patients.

Methods: This was a prospective randomized study that enrolled consecutive ASA I-III patients scheduled for various elective surgeries under general anesthesia. The patients were divided into two groups: Group D (diabetic, n=21) and Group ND (non-diabetic, n=21). Heart rate variability analyses were performed using a Norav-800 Holter on the day before surgery. On the day of the operation, after premedication and monitoring, general anesthesia was induced with etomidate. Hemodynamic parameters were measured before induction (T1), after induction (T2), and 2 min (T3), 5 min (T4), and 10 min (T5) after endotracheal intubation. Hemodynamic changes and heart rate variability were compared between the two groups.

Results: Group D showed a statistically significant decrease in systolic arterial pressure values at T2, T4, and T5 compared to baseline values ($p<0.001$), while Group ND showed no significant differences in any period. Diastolic blood pressure decreased significantly in Group D compared to baseline values in the preintubation period ($p<0.001$), but there was no significant change in Group ND. Heart rate did not significantly differ between the two groups during any measurement period, and there was no correlation between heart rate variability and hemodynamic changes.

Conclusion: The results suggest that etomidate anesthesia induction provides hemodynamic stability in patients with type 2 diabetes mellitus. Despite its potential utility, heart rate variability measured during resting conditions may not provide sufficient diagnostic accuracy for predicting the presence of autonomic neuropathy, particularly in individuals with diabetes mellitus. Therefore, additional measures may be needed for early detection of cardiac autonomic dysfunction in these patients.

Keywords: Autonomic dysfunction, etomidate, diabetes mellitus, heart rate variability

INTRODUCTION

Diabetes mellitus (DM) is presently recognized as the foremost endocrine ailment worldwide, with a heightened demand for surgical interventions and ICU admissions when compared to the nondiabetic population. This clinical observation highlights the pressing need for continued research and development of improved management strategies for patients with DM.[1] Cardiovascular autonomic neuropathy (CAN) is a common and severe complication of diabetes. It has been reported that CAN is present in 22.1% of type 2 diabetics and 16.8% of type 1 diabetics.[2] CAN is caused by damage to the autonomic nerve fibers that supply the heart and blood vessels. This damage to nerve fibers leads to disturbances in heart rate control and hemodynamics. Clinically, it manifests itself as postural hypotension, exercise intolerance, intraoperative cardiovascular lability, and silent myocardial ischemia/infarction in diabetic patients.[3] Cardiovascular reflex tests are sensitive, reproducible, simple, and noninvasive tests that provide a comprehensive diabetic cardiovascular autonomic neuropathy assessment. These include heart rate at rest, beat-to-beat heart rate variability, blood pressure response to the Valsalva maneuver, heart rate and systolic blood pressure during standing and diastolic blood pressure during prolonged exercise. Reduced 24-hour heart rate variability is a new test that is more sensitive than the standard reflex test and detects cardiac autonomic dysfunction earlier. The recording of 24-hour heart rate

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variability can reveal abnormal circadian rhythms regulated by sympathovagal activity. The high-frequency component of heart rate variability is decreased in vagal dysfunction. On the other hand, the low-frequency and very low-frequency components decrease sympathetic dysfunction. In advanced cardiac autonomic neuropathy, all three components are decreased, as is the ratio between low and high frequencies, which indicates sympathovagal balance.[4]

Cardiovascular instability has been shown to increase during anesthesia, and abnormal cardiovascular responses can occur during anesthetic induction and intubation in patients with CAN.[3] These patients have been shown to have a greater need for surgical intervention and intensive care hospitalization than nondiabetic patients and to have higher perioperative mortality and morbidity.[1] Etomidate is a fast-acting hypnotic used for the induction of anesthesia. Etomidate administration results in minimal hemodynamic changes while maintaining hemodynamic stability by preserving sympathetic outflow and autonomic reflexes.[5]

Hemodynamic instability that may occur during the induction of anesthesia in diabetic patients may make etomidate a suitable option for these patients. We aimed to compare the hemodynamic effects during anesthesia induction and intubation in type 2 diabetic and nondiabetic patients.

METHODS

After patient consent was obtained, elective surgery requiring endotracheal intubation was performed in 42 patients enrolled in the ASA I - III score group. The study was planned as a prospective, randomized, single-blind trial. Patients with uncontrolled hypertension, type 1 diabetes and another condition causing hyperglycemia, hepatic or renal insufficiency, an endocrine or metabolic disorder other than diabetes mellitus, a known allergy to the drugs to be used, and patients in whom difficult intubation was contemplated were excluded from the study. According to their hospitalization date, the patients were divided into two groups of 21 each. Those with type 2 diabetes whose blood glucose was controlled by oral antidiabetics were classified as Group D, whereas those without DM were classified as Group ND. HbA1c was measured in diabetic patients. Heart rate variability analysis was performed the day before surgery, according to the recommendations of the HRV Task Force.[6] The 5-minute ECG recording with the Norav-800 Holter was recorded on the SD memory card and transferred to the computer environment. Heart rate variability was determined by analyzing data on the NH-300 operating system based on time and rate.

The patient, who received 1 mg of midazolam in the preoperative room, was brought to the operating table and monitored with electrocardiography, noninvasive blood pressure, and peripheral oxygen saturation. For premedication, 1 mg of midazolam was administered. In induction, 1 mcg/kg fentanyl, 0.3 mg/kg etomidate and 0.6 mg/kg rocuronium were administered. After muscle relaxation, endotracheal intubation was performed. After endotracheal intubation, sevoflurane was administered at a concentration of 2% and 4 l/min at a rate of 50-50% in a flow rate O2-air mixture to maintain anesthesia. Hemodynamic parameters such as systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and heart rate (HR) were measured and recorded.

Hemodynamic parameters were measured after monitoring (T1), before induction (T2), and 2 minutes (T3), 5 minutes (T4), and 10 minutes (T5) after endotracheal intubation. Hemodynamic alterations and heart rate variability were evaluated and compared between both groups.

Statistical Analysis

The data obtained were analyzed using the prepackaged statistical program SPSS 16.0. The chi-square test was used to compare the quantitative data between groups, and Student's t test was used to compare the qualitative data. Two-way analysis of variance was performed for a within-group comparison of hemodynamic data. The variance distribution was evaluated with the Kolmogorov–Smirnov test. Data are expressed as the mean ± standard deviation or median (interquartile range). The accepted level of significance in this study was $p<0.05$.

RESULTS

There was no difference between the weight, height, sex, and ASA group distribution groups. The age of the patients in group D was significantly higher than that in group ND ($p<0.05$). Fasting blood glucose levels and percent HbA1c were significantly higher in diabetic patients than in nondiabetic patients ($p<0.05$) (**Table 1**).

Table 1. Demographic characteristics of the groups

	Goup D (n=21)	Goup ND (n=21)
Age (year)	53.3 ± 11.7	44.7 ± 13.9
Weight (kg)	81.6 ± 10.6	73.9 ± 14.9
Gender (F/M)	16/5	16/5
Fasting blood glucouse	115 ± 22	89 ± 17
HbA1c (%)	6.94 ± 0.9	5.17 ± 0.81
ASA II/III	18/3	14/7

While the SAP values measured in the T2, T4, and T5 periods were statistically significantly lower in Group D than in the baseline values ($p<0.001$), no significant difference from the baseline values was observed in Group ND in any period (**Figure 1**).

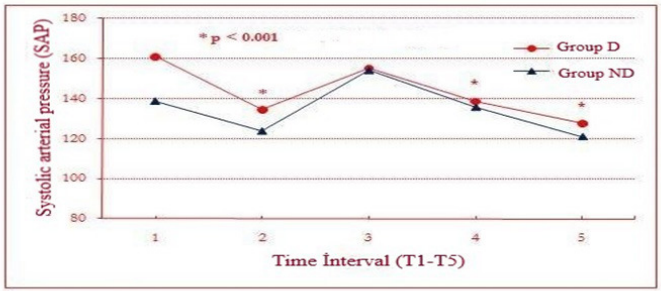

Figure 1. SAP values according to measurement periods, after monitoring (T1), before induction (T2), 2th minute (T3), 5th minute (T4), 10 minutes (T5) after endotracheal intubation.

There was no significant difference in DAP values at each measurement period between the two groups. In Group D, there was a significant decrease in DAP compared with

baseline values in the period before intubation (p<0.001). There was no significant change in the other measurement periods and Group ND (**Figure 2**).

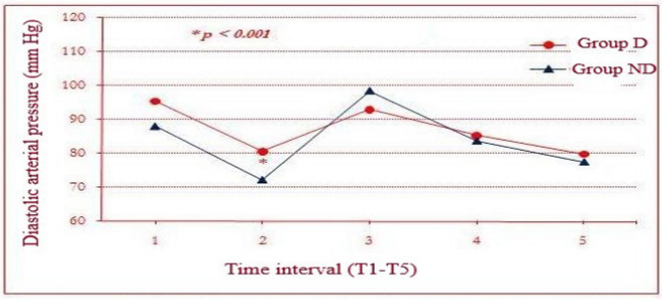

Figure 2. Diastolic arterial pressure values for measurement periods after monitoring (T1), before induction (T2), 2th minute (T3), 5th minute (T4), 10 minutes (T5) after endotracheal intubation.

Group D had a considerably higher baseline MAP than Group ND (p<0.001). Other periods showed no notable differences. It was found that the MAP values in Group D significantly decreased in the T2, T4, and T5 intervals compared to baseline values (p<0.001). In Group ND, there was a significant decrease in MAP in the T2 interval compared to baseline values, while a significant increase was observed in the postintubation period (p<0.01) (**Figure 3**).

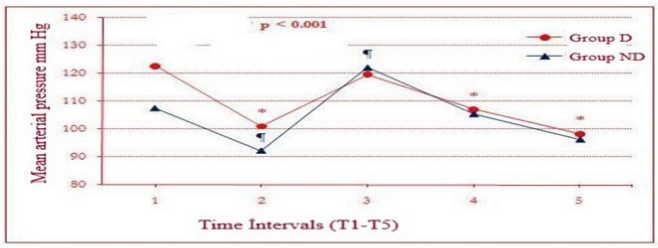

Figure 3. MAP values according to measurement periods. 1.Baseline 2. Before intubation 3. 2 minutes after intubation 4. 5 minutes after intubation 5. 10 minutes after intubation.

There were no significant differences observed in heart rate between the two study groups throughout the measurement periods, and no relationship was identified between heart rate variability and hemodynamic changes (**Table 2, 3**).

Table 2. HRV analysis results of the groups

	Group D (n=21)		Group ND (n=21)	
	Mean	Median	Mean	Median
SDNN	137.73	123.7	134.79	128.2
RMSSD	34.83	20.73	32.56	22.1
Triangular index	4.26	3.75	4.75	4.45
VLF.nu	269.72	253.26	277.13	259.55
LF.nu	178.59	164.25	175.14	158.18
HF.nu	127.65	122.49	127.42	126.57
LF/HF	1.57	1.57	1.6	1.59

Table 3. Comparison of HRV in patients with and without hypotension

	Group H (n=11)		Group NH (n=31)	
	Mean	Median	Mean	Median
SDNN	137.1	123.6	136	130.9
RMSSD	40.6	18.1	37.9	20.1
Triangular index	3.92	3.74	4.71	4.14
VLF.nu	283.3	284.6	287.13	260.4
LF.nu	205.8	205.2	195.14	187.13
HF.nu	130.5	122.5	128.16	126.61
LF/HF	1.81	1.78	1.6	1.57

DISCUSSION

Cardiovascular autonomic neuropathy is a significant long-term complication of diabetes mellitus. This can lead to hemodynamic instability during the induction and maintenance of anesthesia. Etomidate preserves sympathetic outflow and autonomic reflexes in induction. Keyl et al.[7], in their study using etomidate together with HRV analysis in 60 patients, 30 of whom had diabetes and who underwent coronary artery bypass grafting, concluded that autonomic dysfunction during anesthetic induction does not require hemodynamic instability. We reached a similar conclusion. The most important finding of our study was that both diabetic and nondiabetic patients had significant decreases in MAP compared to baseline values after anesthetic induction with etomidate. These decreases were less pronounced than in the Keyl study and, although statistically significant, were not clinically significant. The most significant MAP decreases after etomidate anesthetic induction identified in the study by Keyl et al.[8] may be because of the more pronounced autonomic dysfunction in patients with myocardial perfusion defects.

Induction of anesthesia in people with diabetes should always be considered an aberrant cardiovascular response. According to Linstedt et al.[9], the findings of their study compared circulatory changes in diabetic and nondiabetic patients undergoing eye surgery. They contend that the Valsalva technique, deep breathing, and monitoring heart rate fluctuations while seated can help identify these individuals. Latson et al.[10] reported that the incidence of hypotension increased during the induction of anesthesia in patients with autonomic reflex dysfunction. The study conducted by Burgos et al.[11] aimed to evaluate the incidence of intraoperative cardiac morbidity among diabetic patients undergoing elective ophthalmic surgery. In their investigation, 38 patients were included, of whom 17 were diagnosed with diabetes mellitus. The authors reported significantly elevated reductions in blood pressure and heart rate during anesthesia induction among the diabetic population. Moreover, diabetic patients necessitated a higher dose of intraoperative vasopressors. The results suggest that preoperative assessment of autonomic functions using conventional methods may aid in identifying patients at risk of cardiac morbidity. Thiopental was used for anesthesia induction and was administered at a dose of 3-5 mg/kg in the study. Vohra et al.[12] conducted a study to investigate the impact of diabetes mellitus on cardiovascular responses to anesthesia induction and tracheal intubation. All diabetic patients showed abnormal results in standard cardiovascular autonomic function tests. There was no significant difference in preoperative cardiovascular status between the two groups. After induction of anesthesia, both groups showed a decrease in mean arterial pressure and vascular resistance, but the

diabetic group's heart rate did not change, and the cardiac index decreased. After tracheal intubation, the diabetic group exhibited a more significant increase in mean arterial pressure, vascular resistance, and heart rate than the control group. This suggests that an increased pressure response to tracheal intubation in diabetic patients may be indicative of autonomic dysfunction.

We used HRV analysis instead of traditional autonomic neuropathy testing because it takes less time. Diabetic and nondiabetic subjects had the same time and frequency-based characteristics. Again, there was no difference in HRV between subjects with a mean blood pressure drop-off over 30% (Group H) and those without (Group NH) (**Table 3**). HRV analysis is an indicator used in recent years in patients undergoing spinal anesthesia to determine the risk of hypotension. It has been reported that the risk of hypotension is higher in cases with an LF/HF ratio of 2.5 or more. Although such a precise value has not been reported to determine the risk of hypotension after intravenous induction, the existence of an association between HRV analysis and hypotension after induction of anesthesia has been reported.[13,14] In contrast, we did not find any association between hypotension and the results of HRV analysis. In the study by Knuettgen et al.[13], the difference between HRV results in diabetic patients who developed hypotension and those who did not may be because thiopental was used as an induction agent. Sympathetic outflow and autonomic reflexes are preserved because of the induction of anesthesia with etomidate. Schwarzkopf et al.[15] conducted a study to compare the efficacy of preanesthesia administration of etomidate or midazolam in preventing etomidate-induced myoclonus. The study included 60 premedicated patients who were divided into three groups of 20 each. The first group received 0.05 mg/kg IV etomidate 90 seconds before induction, the second group received 0.015 mg/kg IV midazolam, and the third group received IV normal saline as a placebo. Anesthesia was induced with sufentanil and rocuronium one minute after the onset of hypnosis. Myoclonic movements were observed from the preinduction period of midazolam or etomidate administration to the end of anesthesia and were recorded on a scale of 0 to 3. The results showed that myoclonus was significantly lower (4 out of 20 patients) in those who received 0.015 mg/kg midazolam before induction with etomidate. The current study involved the administration of 1-1.5 mg midazolam and 1 mg/kg fentanyl IV to all patients 3-5 minutes before anesthesia induction. Slow induction of etomidate within 20 seconds did not result in myoclonus in any of the 20 patients. The results indicate that premedication with fentanyl and midazolam, along with a slow injection of etomidate, may prevent myoclonus.

CONCLUSION

As a result, cardiovascular autonomic neuropathy (CAN) is a common and severe complication of diabetes that can lead to hemodynamic instability during anesthesia. HRV is a new test that is more sensitive than the standard reflex test and detects cardiac autonomic dysfunction earlier. In this study, the hemodynamic effects during anesthesia induction and intubation were compared between type 2 diabetic and nondiabetic patients. Etomidate administration resulted in minimal hemodynamic changes while maintaining hemodynamic stability by preserving sympathetic outflow and autonomic reflexes in diabetic patients. The study concluded that etomidate may be a suitable option for anesthesia induction in diabetic patients with CAN. Furthermore, we feel that HRV evaluated at rest may not be adequate for detecting autonomic neuropathy in some instances.

Acknowledgments

This article is a publication of the anesthesiology and reanimation specialty thesis of Alparslan Koç, which was completed in 2010.

This article was presented orally at the 7th Balkan States Anesthesia Days (ARUD 2021) as summary text, and at the 5th International Health Science and Life Congress (IHSLC 2022) as full text.

ETHICAL DECLARATIONS

Ethics Committee Approval: This article is a publication of the anesthesiology and reanimation specialty thesis of Alparslan Koç, which was completed in 2010. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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